

APR 14 2004

Date of Approval: _____

FREEDOM OF INFORMATION SUMMARY
ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-361

Acepromazine Maleate Injection
(acepromazine maleate)

Tranquilizer

For use as an aid in tranquilization and as a preanesthetic agent
in dogs, cats, and horses.

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

ANADA 200-361

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

- a. File Number: ANADA 200-361
- b. Sponsor: Boehringer Ingelheim Vetmedica, Inc.
2621 North Belt Highway
St. Joseph, MO 64506-2002

Drug Labeler Code: 000010
- c. Established Name: Acepromazine maleate
- d. Proprietary Name: Acepromazine Maleate Injection
- e. Dosage Form: Sterile solution
- f. How Supplied: 50 mL multidose vials
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: 10 mg acepromazine maleate per mL of sterile finished product
- i. Route of Administration: Intravenous, intramuscular or subcutaneous injection
- j. Species/Class: Dogs, cats, and horses
- k. Recommended Dosage: The dosage should be individualized, depending upon the degree of tranquilization required. As a general rule, the dosage requirement in mg/lb of body weight decreases as the weight of the animal increases. The following schedule may be used as a guide to intravenous, intramuscular, or subcutaneous injection:
- Dogs – 0.25 mg-0.5 mg/lb of body weight
Cats – 0.5-1 mg/lb of body weight
Horses – 2-4 mg/100 lb of body weight
- Intravenous doses should be administered slowly, and a period of at least 15 minutes should be allowed for the drug to take full effect.

1. Pharmacological Category: Tranquilizer
- m. Indications:
- Dogs and Cats: Acepromazine Maleate Injection can be used as an aid in controlling intractable animals during examination, treatment, grooming, x-ray and minor surgical procedures; to alleviate itching as a result of skin irritation; as an antiemetic to control vomiting associated with motion sickness. Acepromazine Maleate Injection is particularly useful as a preanesthetic agent (1) to enhance and prolong the effects of barbiturates, thus reducing the requirements for general anesthesia; (2) as an adjunct to surgery under local anesthesia.
- Horses: Acepromazine Maleate Injection can be used as an aid in controlling fractious animals during examination, treatment, loading and transportation. Particularly useful when used in conjunction with local anesthesia for firing, castration, neurectomy, removal of skin tumors, ocular surgery and applying casts.
- n. Pioneer Product: PROMACE Injectable; acepromazine maleate; NADA 015-030; Fort Dodge Animal Health, Division of Wyeth

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

Ordinarily, the ANADA sponsor shows the generic product is bioequivalent to the pioneer, which has been shown to be safe and effective. If bioequivalence is demonstrated through a clinical endpoint study, then a tissue residue study to establish the withdrawal time for the generic product should also be conducted. For certain dosage forms, the agency will grant a waiver from the requirement of an *in vivo* bioequivalence study. (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 9, 2002).

Based on the formulation characteristics of the generic product, Boehringer Ingelheim Vetmedica, Inc. was granted a waiver from the requirement of an *in vivo* bioequivalence study for the generic product Acepromazine Maleate Injection. The generic product is administered as an intravenous, intramuscular or subcutaneous injection, contains the same active ingredient in the same concentration and dosage form as the pioneer product, and contains no inactive ingredients that may significantly affect the absorption of the active ingredient. The pioneer product PROMACE Injectable (acepromazine maleate), the subject of Fort Dodge Animal Health, Division of Wyeth, NADA 015-030, was approved on April 8, 1964.

3. HUMAN SAFETY:

This drug is intended for use in dogs, cats and horses, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the Act and demonstrates that Acepromazine Maleate Injection, when used under its proposed conditions of use, is safe and effective for its labeled indications.

5. ATTACHMENTS:

Facsimile generic labeling and currently approved pioneer labeling are attached as follows:

Generic Labeling for ANADA 200-361:

Acepromazine Maleate Injection; vial labels and package insert

Pioneer Labeling for NADA 015-030:

PROMACE Injectable; vial labels and package insert

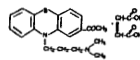
ANADA 200-361, Approved by FDA

Acepromazine Maleate Injection

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: Acepromazine maleate USP, a potent neuroleptic agent with a low order of toxicity, is of particular value in the tranquilization of dogs, cats and horses. Its rapid action and lack of hypnotic effect are added advantages. According to Baker,¹ the scope of possible applications for this compound in veterinary practice is only limited by the imagination of the practitioner.

Chemistry: Acepromazine [10-[3-(dimethylamino)propyl]phenothiazin-2-yl-methyl ketone] Maleate, USP has the following chemical structure:



Actions: Acepromazine maleate has a depressant effect on the central nervous system and therefore, causes sedation, muscular relaxation and a reduction in spontaneous activity. It acts rapidly, exerting a prompt and pronounced calming effect.

Indications: Dogs and Cats: Acepromazine Maleate Injection can be used as an aid in controlling intractable animals during examination, treatment, grooming, x-ray and minor surgical procedures; to alleviate itching as a result of skin irritation; as an antiemetic to control vomiting associated with motion sickness. Acepromazine Maleate Injection is particularly useful as a preanesthetic agent (1) to enhance and prolong the effects of barbiturates, thus reducing the requirements for general anesthesia; (2) as an adjunct to surgery under local anesthesia.

Horses: Acepromazine Maleate Injection can be used as an aid in controlling fractious animals during examination, treatment, loading and transportation. Particularly useful when used in conjunction with local anesthesia for flying, castration, neutering, removal of skin tumors, ocular surgery and applying casts.

Contraindications: Phenothiazines may potentiate the toxicity of organophosphates and the activity of procaine hydrochloride. Therefore, do not use Acepromazine Maleate Injection to control tremors associated with organic phosphate poisoning. Do not use in conjunction with organophosphorus vermicides or ectoparasitides, including flea collars. Do not use with procaine hydrochloride.

Warning: Not for use in animals intended for food.

Precautions: Tranquilizers are potent central nervous system depressants and they can cause marked sedation with suppression of the sympathetic nervous system. Tranquilizers can produce prolonged depression or motor restlessness when given in excessive amounts or when given to sensitive animals. Tranquilizers are additive in action to the actions of other depressants and will potentiate general anesthesia. Tranquilizers should be administered in smaller doses and with greater care during general anesthesia and also to animals exhibiting symptoms of stress, debilitation, cardiac disease, sympathetic blockade, hypovolemia or shock. Acepromazine maleate, like other phenothiazine derivatives, is detoxified in the liver; therefore, it should be used with caution in animals with a previous history of liver dysfunction or leukopenia. Hypertension can occur after rapid intravenous injection causing cardiovascular collapse.

Epinephrine is contraindicated for treatment of acute hypertension produced by phenothiazine-derivative tranquilizers since further depression of blood pressure can occur. Other pressor amines, such as norepinephrine or phenylephrine, are the drugs of choice. In horses, paralysis of the retractor penis muscle has been associated with the use of phenothiazine-derivative tranquilizers. Such cases have occurred following the use of Acepromazine Maleate Injection. This risk should be duly considered prior to the administration to male horses (castrated and uncastrated). When given, the dosage should be carefully limited to the minimum necessary for the desired effect. At the time of tranquilization, it is not possible to differentiate between reversible protrusion of the penis (a normal clinical sign of narcosis) and the irreversible paralysis of the retractor muscle. The cause of this side reaction has not been determined. It has been postulated that such paralysis may occur when a tranquilizer is used in conjunction with testosterone (or its esters). Accidental intracardial injection in horses can produce clinical signs ranging from discoloration to convulsive seizure and death.

Caution: A few rare but serious occurrences of idiosyncratic reactions to Acepromazine may occur in dogs following oral or parenteral administration. These potentially serious adverse reactions include behavioral disorders in dogs such as aggression, biting/chewing, and nervousness.

Administration and Dosage: The dosage should be individualized, depending upon the degree of tranquilization required. As a general rule, the dosage requirement in mg/lb of body

Cats: 0.5-1 mg/lb of body weight.
Horses: 2-4 mg/100 lb of body weight.

N/doses should be administered slowly, and a period of at least 15 minutes should be allowed for the drug to take full effect.

How Supplied: Each ml. contains 10 mg acepromazine maleate, sodium citrate 0.36%, citric acid 0.075%, benzyl alcohol 1% and water for injection, USP in 30 ml. vials.

Store at controlled room temperature, 59°-86°F (15°-30°C).

Toxicology: Acute and chronic toxicity studies have shown a very low order of toxicity.

Acute Toxicity: The LD₅₀ dose of acepromazine maleate in mice was determined by means of a probit transformation with the following results:

Intravenous route	61.27 mg/kg
Subcutaneous route	130.5 mg/kg
Oral route	256.8 mg/kg

Chronic Toxicity Tests: In rats revealed no deleterious effects on renal or hepatic function or on hemopoietic activity. In several groups of two male and two female beagle hounds treated for six months with daily oral doses of 20 to 40 mg/kg, no untoward effects were encountered. Hematologic studies and urinalysis gave values within normal limits. Another group of four dogs, given gradually increasing oral doses up to a level of 220 mg/kg daily and reaching a total daily dose of 2.2 g per dog, showed some signs of pulmonary edema and hyperemia of the internal organs, but no animal died. When administered intramuscularly, Acepromazine Maleate Injection causes a brief sensation of stinging comparable with that observed with other phenothiazine tranquilizers.

Clinical Data: Controlled clinical studies in the United States and Canada have demonstrated the effectiveness and safety of Acepromazine Maleate Injection as a tranquilizer. Good to excellent results were reported^{4,5} in dogs, cats and horses given Acepromazine Maleate Injection for restraint during examination, treatment and minor surgery and for preanesthetic sedation. In dogs, the drug reportedly helps control convulsions associated with distemper. In horses, Bauman⁶ had good results using the drug as an aid in the control of painful spasms due to colic. Other practitioners^{7,8} found the drug useful as a preanesthetic sedative for nervous or aggressive horses, but it had to be administered while the animals were quiet and not in an excited state. In a trial⁹ on more than 200 horses with a wide variety of disorders, Acepromazine Maleate Injection proved to be both effective and safe.

References:

1. Baker, J.M.: Paper presented at the Ontario Veterinary Association meeting, held in Toronto, Canada, 1958.
2. Pharmacology Reports, Ciba-Geigy Laboratories, Paris, France.
3. Stegen, M.G.: Pharmacology Report, Ayerst Laboratories, 1958.
4. Veterinary Medical Records, Ayerst Laboratories.
5. Foley, J.T.: Clinical Reports to Ayerst Laboratories, 1963.
6. Bauman, W.G.: Clinical Reports to Ayerst Laboratories, 1963.
7. Ford, R.W.: In Equine Panel Report, Mod. Vet. Pract. 40:45 (Nov. 1) 1959.
8. Baldwin, R.: In Equine Panel Report, Mod. Vet. Pract. 40:46 (Nov. 1) 1959.
9. Danks, T.E.: Clinical Reports to Ayerst Laboratories, 1963.

670011-02-0308

W. H. Green
Engelheim

44713

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Lot No.: Exp. Date:

000023

NDC 0895-3020-01

USUAL DOSAGE: Dogs — 0.25 mg up to 0.5 mg/lb of body weight. Cats — 0.5 mg up to 1 mg/lb of body weight. Horses — 2 mg up to 4 mg/100 lbs of body weight.
READ PACKAGE INSERT.

Store at controlled room temperature 15° to 30°C (59° to 86°F).
Acepromazine (10-[3-(dimethylamino) propyl] phenothiazin-2-yl-methyl ketone) Maleate, USP
This sterile aqueous solution also contains sodium citrate 0.36%, citric acid 0.076%, benzyl alcohol 1% and water for injection, USP.
U.S. Pat. No. 3,330,628

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

PromAce® Injectable
ACEPROMAZINE MALEATE INJECTION, USP

FORT DODGE

A Sterile Solution for
Intravenous, Intramuscular or
Subcutaneous Injection
Equivalent to 10 mg/mL Acepromazine Maleate, USP
50 mL

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA 16-090, Approved by FDA

Lot
Exp.





FORT DODGE®

PromAce[®] Injectable

ACEPROMAZINE MALEATE INJECTION, USP

PromAce[®] Tablets

ACEPROMAZINE MALEATE TABLETS, USP

NADA 15-030, Approved by FDA
NADA 32-702, Approved by FDA

CAUTION

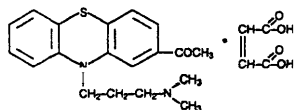
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

PROMACE (acepromazine maleate, USP), a potent neuroleptic agent with a low order of toxicity, is of particular value in the tranquilization of dogs, cats and horses. Its rapid action and lack of hypnotic effect are added advantages. According to Baker,¹ the scope of possible applications for this compound in veterinary practice is only limited by the imagination of the practitioner.

CHEMISTRY

Acepromazine [10-[3-(dimethylamino) propyl] phenothiazin-2-yl-methyl ketone] Maleate, USP has the following chemical structure:



ACTIONS

PROMACE has a depressant effect on the central nervous system and, therefore, causes sedation, muscular relaxation and a reduction in spontaneous activity. It acts rapidly, exerting a prompt and pronounced calming effect.

INDICATIONS

Dogs and Cats: PROMACE Injectable and Tablets can be used as an aid in controlling intractable animals during examination, treatment, grooming, x-ray and minor surgical procedures; to alleviate itching as a result of skin irritation; as an antiemetic to control vomiting associated with motion sickness.

PROMACE Injectable is particularly useful as a preanesthetic agent (1) to enhance and prolong the effects of barbiturates, thus reducing the requirements for general anesthesia; (2) as an adjunct to surgery under local anesthesia.

Horses: PROMACE Injectable can be used as an aid in controlling fractious animals during examination, treatment, loading and transportation. Particularly useful when used in conjunction with

local anesthesia for firing, castration, neurectomy, removal of skin tumors, ocular surgery and applying casts.

CONTRAINDICATIONS

Phenothiazines may potentiate the toxicity of organophosphates and the activity of procaine hydrochloride. Therefore, do not use PROMACE (acepromazine maleate, USP) to control tremors associated with organic phosphate poisoning. Do not use in conjunction with organophosphorus vermifuges or ectoparasiticides, including flea collars. Do not use with procaine hydrochloride.

WARNING

Not for use in animals intended for food.

PRECAUTIONS

Tranquilizers are potent central nervous system depressants and they can cause marked sedation with suppression of the sympathetic nervous system.

Tranquilizers can produce prolonged depression or motor restlessness when given in excessive amounts or when given to sensitive animals.

Tranquilizers are additive in action to the actions of other depressants and will potentiate general anesthesia. Tranquilizers should be administered in smaller doses and with greater care during general anesthesia and also to animals exhibiting symptoms of stress, debilitation, cardiac disease, sympathetic blockade, hypovolemia or shock. PROMACE, like other phenothiazine derivatives, is detoxified in the liver; therefore, it should be used with caution in animals with a previous history of liver dysfunction or leukopenia.

Hypotension can occur after rapid intravenous injection causing cardiovascular collapse.

Epinephrine is contraindicated for treatment of acute hypotension produced by phenothiazine derivative tranquilizers since further depression of blood pressure can occur. Other pressor amines, such as norepinephrine or phenylephrine, are the drugs of choice.

In horses, paralysis of the retractor penis muscle has been associated with the use of phenothiazine-derivative tranquilizers. Such cases have occurred following the use of PROMACE. This risk should be duly considered prior to the administration of PROMACE to male horses (castrated and uncastrated). When given, the dosage should be carefully limited to the minimum necessary for the desired effect. At the time of tranquilization, it is not possible to differentiate between reversible protrusion of the penis (a normal clinical sign of narcosis) and the irreversible paralysis of the retractor muscle. The cause of this side reaction has not been determined. It has been postulated that such paralysis may occur when a tranquilizer is used in conjunction with testosterone (or in stallions).

Accidental intracarotid injection in horses can produce clinical signs ranging from disorientation to convulsive seizures and death.

CAUTION

A few rare but serious occurrences of idiosyncratic reactions to Acepromazine may occur in dogs following oral or parenteral administration. These potentially serious adverse reactions

include behavioral disorders in dogs such as aggression, biting/chewing, and nervousness.

ADMINISTRATION AND DOSAGE

The dosage should be individualized, depending upon the degree of tranquilization required. As a general rule, the dosage requirement in mg/lb of body weight decreases as the weight of the animal increases.

PROMACE Injectable (acepromazine maleate Injection, USP)

May be given intravenously, intramuscularly or subcutaneously. The following schedule may be used as a guide to IV, IM or SC injections:

Dogs: 0.25–0.5 mg/lb of body weight

Cats: 0.5–1 mg/lb of body weight

Horses: 2–4 mg/100 lb of body weight

IV doses should be administered slowly, and a period of at least 15 minutes should be allowed for the drug to take full effect.

PROMACE Tablets (acepromazine maleate tablets, USP)

Dogs: 0.25–1 mg/lb of body weight. Dosage may be repeated as required.

Cats: 0.5–1 mg/lb of body weight. Dosage may be repeated as required.

HOW SUPPLIED

Each mL contains 10 mg PROMACE (acepromazine maleate, USP). (Also contains sodium citrate 0.36%, citric acid 0.075%, benzyl alcohol 1% and Water for Injection, USP) in 50 mL vials.

Each light orange tablet contains 5 mg of PROMACE and is available in bottles of 100.

Each orange tablet contains 10 mg of PROMACE and is available in bottles of 100 and 500.

Each yellow tablet contains 25 mg of PROMACE and is available in bottles of 100 and 500.

NDC 0856-3020-01 — 10 mg/mL — 50 mL vial

NDC 0856-0040-01 — 5 mg — bottles of 100

NDC 0856-0070-01 — 10 mg — bottles of 100

NDC 0856-0070-02 — 10 mg — bottles of 500

NDC 0856-0100-01 — 25 mg — bottles of 100

NDC 0856-0100-02 — 25 mg — bottles of 500

Store at controlled room temperature 15° to 30°C (59° to 86°F).

TOXICOLOGY

Acute and chronic toxicity studies have shown a very low order of toxicity.

Acute toxicity: The LD₅₀ dose of PROMACE in mice was determined by means of a probit transformation with the following results:²

Intravenous route —	61.37 mg/kg
Subcutaneous route —	130.5 mg/kg
Oral route —	256.8 mg/kg

Chronic toxicity: Tests³ in rats revealed no deleterious effects on renal or hepatic function or on hemopoietic activity. In several groups of two male and two female beagle hounds treated for six months with daily oral doses of 20 to 40 mg/kg, no untoward

effects were encountered. Hematologic studies and urinalysis gave values within normal limits. Another group of four dogs, given gradually increasing oral doses up to a level of 220 mg/kg daily and reaching a total daily dose of 22 g per dog, showed some signs of pulmonary edema and hyperemia of the internal organs, but no animal died.

When administered intramuscularly, PROMACE (acepromazine maleate, USP) causes a brief sensation of stinging comparable with that observed with other phenothiazine tranquilizers.

CLINICAL DATA

Controlled clinical studies in the United States and Canada have demonstrated the effectiveness and safety of PROMACE as a tranquilizer.

Good to excellent results were reported^{1,4,5} in dogs, cats and horses given PROMACE Injectable for restraint during examination, treatment and minor surgery and for preanesthetic sedation. In dogs, the drug reportedly helps control convulsions associated with distemper.

In both dogs and cats, good to excellent results were obtained⁴ when PROMACE Tablets were used to control nervousness, excessive vocalization, neurotic and excitable behavior, vomiting associated with motion sickness, coughing and itching caused by dermatitis.

In horses, Bauman⁶ had good results using the drug as an aid in the control of painful spasms due to colic.

Other practitioners^{7,8} found the drug useful as a preanesthetic sedative for nervous or aggressive horses, but it had to be administered while the animals were quiet and not in an excited state. In a trial⁹ on more than 200 horses with a wide variety of disorders, PROMACE Injectable proved to be both effective and safe.

REFERENCES

1. Baker, J.M.: Paper presented at the Ontario Veterinary Association meeting, held in Toronto, Canada, 1958.
2. Pharmacology Reports, ClinByla Laboratories, Paris, France.
3. Stegen, M.G.: Pharmacology Report, Ayerst Laboratories, 1958.
4. Veterinary Medical Records, Ayerst Laboratories.
5. Foley, J.T.: Clinical Reports to Ayerst Laboratories, 1963.
6. Bauman, W.G.: Clinical Reports to Ayerst Laboratories, 1963.
7. Ford, R.W.: in Equine Panel Report, *Mud. Vet. Pract.* 40:45 (Nov. 1) 1959.
8. Baldwin, R.: in Equine Panel Report, *Mod. Vet. Pract.* 40:46 (Nov. 1) 1959.
9. Dunkin, T.E.: Clinical Reports to Ayerst Laboratories, 1963.

Manufactured for
Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA
by Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA
(Injection)

Ayerst Laboratories, Inc.
Rouses Point, NY 12979
(Tablets)